

## REMARKS

Attached hereto is a marked-up version of the changes made to the claims by the above amendment. The attached pages begin with the caption "**Version with markings to show changes made.**"

Claims 36-87 were pending in the present application. Applicants have amended claims 36 and 60 without altering the scope of the claims from that which was originally intended. Applicants have also cancelled claim 62 in favor of amended claim 60, and added new claims 88-93 and 95, which are dependent upon claim 60. New claims 88-93 direct the subject matter of claim 60 to the subject matter of cancelled claims 78-87 without affecting the election with traverse. New claim 94 is dependent from claim 54. The new claims are supported by the claims as filed in the preliminary amendment, and do not contain new matter. Thus, claims 36-41, 44-52, 60-61, and 88-95 are pending in the present application.

The above amendments have been made are for reasons related to business considerations and to tailor the claims to currently contemplated embodiments of the invention and not in acquiescence to any reason related to patentability.

### Response to Restriction

Applicants affirm the election made with traverse to prosecute the invention of N'-lysylspermine. Applicant respectfully disagree, however, with the withdrawal of dependent claims 42, 43, 53-59, and 62-87 as "not embracing the elected species and/or because they contained non-examined species" (Office Action, page 2). As the Examiner is no doubt aware, dependent claims contain all of the limitations of the claims from which they depend.

Claims 42 and 43 do not exclude N'-lysylspermine and are dependent upon claim 41, which has been examined. Similarly, claims 53-59 do not exclude N'-lysylspermine and are dependent from claim 52, which has been examined. Likewise, claims 63-68 do not exclude N'-lysylspermine and are dependent from claims 60 and 61, which have been examined. Finally, claims 69-77 do not exclude N'-lysylspermine and are dependent from claims 36-39, which have also been examined. Because withdrawn claims 42, 43, 53-59, and 62-77 are dependent from examined claims and do not exclude the elected species, they may not be withdrawn from consideration because they **do** "embrace the elected species". To the extent that they may

“contain non-examined species”, Applicants note that the claims must still be examined to the extent that they encompass the elected species.

Therefore, Applicants respectfully request that withdrawn claims 42-43, 53-59, and 63-77 be rejoined with claims 36-41, 44-52, 60 and 61.

#### The Claims Are Definite

The Examiner rejected claims 36-41, 44-52, 60 and 61 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner suggested that the recitation “or analogue thereof wherein” may be removed without altering the meaning of the claim with respect to the four listed substituents (Office Action, page 3). Applicants are appreciative of the Examiner’s suggestion, and have amended the claims as suggested. The amendment has not changed the scope of the claims. Applicants therefore respectfully request that this rejection be withdrawn.

#### The Claims Are Novel

The Examiner rejected claims 36-41, 44, 60 and 61 under 35 U.S.C. § 102(b), as allegedly being anticipated by Cherksey *et al.*, (WO 91/00853). In particular, the Examiner states that Cherksey *et al.* disclose lysylspermine on page 19 therein. Applicants respectfully traverse because no *prima facie* case of anticipation has been presented.

Claims 36-41 and 44 encompass the D- isomer of lysylspermine. Cherksey *et al.* describe lysylspermine without indication of chirality and so **they do not teach the D- isomer**. In the absence of an express teaching of the D- isomer, Cherksey *et al.* cannot, as a matter of law, anticipate the claims.

To the extent that the instant rejection may be based upon an interpretation that Cherksey *et al.* teach a racemic mixture of the D- and L- isomers, Applicants respectfully point out that it is settled law that disclosure of a racemate (*i.e.*, combination of D and L isomers) does not anticipate claims directed to only one isomer. “[N]ovelty of an optical isomer is not negated by prior art disclosure of its racemate” *In re May and Eddy* 197 U.S.P.Q. 601, 607 (CCPA 1978) (quoting *In re Williams*, 171 F.2d 319, 80 (CCPA 1948)). If Cherksey *et al.* describe racemic lysylspermines, claims 36-41, and 44 are not anticipated as a matter of law. Therefore,

Applicants respectfully request again that this rejection be withdrawn because no *prima facie* case of anticipation has been presented.

Furthermore, Cherksey *et al.* do not anticipate amended claims 60 and 61, which recite the L- isomer of lysylspermine. As noted above, Cherksey *et al.* describe lysylspermine without indication of chirality and so **they do not teach the L- isomer**. In the absence of an express teaching of the L- isomer, Cherksey *et al.* cannot, as a matter of law, anticipate the claims. Nevertheless, and without acquiescing to the Examiner's arguments, Applicants have amended 60 and 61 to emphasize the claims as directed to the inhibition of polyamine transport inhibition. Cherksey *et al.* do not describe methods comprising contacting a cell with a polyamine derivative of the present invention, or a salt thereof, *under conditions such that polyamine transport in the cell is inhibited*. Cherksey *et al.* completely fails to disclose any use relating to polyamine transport inhibition. Therefore, Cherksey *et al.* do not anticipate claims 60 and 61 or any claims dependent therefrom. Applicants therefore respectfully request that this rejection be withdrawn because no *prima facie* case of anticipation has been presented.

#### The Claims Are Non-Obvious

The Examiner also rejected claims 36-41, 44-52, 60 and 61 under 35 U.S.C. § 103(a), as allegedly being unpatentable under Cherksey *et al.*, who disclose the single lysylspermine compound to be a *potential* P-channel activator. The Examiner concedes that the homologues and pharmaceutical forms of the presently claimed invention differ from those compounds described in Cherksey *et al.* (Office Action, page 4). However, the Examiner states that it would have been *prima facie* obvious "to start with the teaching of the cited reference to make positions isomers/homologues thereof and to expect them to be useful as P-channel activators." (Office Action, page 4). Applicants respectfully traverse because no *prima facie* case of obviousness has been presented.

As an initial matter, it appears that the asserted expectation of producing useful P-channel activators is speculative. This follows because Cherksey *et al.* describe the lysylspermine compound to be a *potential* P-channel activator (see page 19, lines 17-20). As such, any "obvious" isomers/homologues of the lysylspermine would at most be expected to be *potential* P-channel activators. Clearly, this amounts to an impermissible assertion of "obvious to try" to obtain additional P-channel activators by producing isomer/homologue compounds that

*potentially* have such activity. Applicants respectfully submit that this is insufficient to support a *prima facie* case of obviousness.

Additionally, the present invention is directed to the use of the claimed compounds to inhibit polyamine transport and/or the inhibition of cell proliferation, which are properties not taught or suggested by Cherksey *et al.* As such, the claimed compounds already display unexpected results over the *potential* P-channel activating compound ("CC") taught by Cherksey *et al.* Such unexpected results are sufficient to prevent the establishment of a *prima facie* case of obviousness (see MPEP 2144.09). This is particularly relevant to claims 60 and 61, which specifically relate to the inhibition of polyamine transport, an unexpected property available with the instant invention but not taught or suggested by Cherksey *et al.*

To the extent that the instant rejection is based upon an alleged obviousness of position isomers and homologues of the single lysylspermine taught by Cherksey *et al.*, Applicants respectfully submit that even the D- isomer (or form) of lysylspermine possesses unexpected properties sufficient to render it non-obvious over the L- isomer.

As indicated in the attached Declaration of Dr. Reitha Weeks ("Weeks Declaration"), the D- form of lysylspermine showed unexpected differences in tissue accumulation in comparison to the L-form of lysylspermine. In particular, the tissue concentrations of the L- and D- forms of lysylspermine when measured from mouse liver, kidney and heart tissues, are significantly different after 13 days. (Weeks Declaration, ¶¶ 6 and 7). Specifically, the concentrations of the D- form were unexpectedly higher than that of the L- form. The higher tissue concentration of the D- form of lysylspermine has significance for the use of the compound in the inhibition of polyamine transport and/or the inhibition of cell proliferation. Higher tissue concentrations permit the use of lower amounts of a compound to achieve the same biological effect, such as polyamine transport inhibition and/or inhibition of cell proliferation, in a tissue.

In light of the unexpected differences in properties between D- and L- lysylspermine, Applicants respectfully submit that claims 36-41, and 44-52 are not obvious over Cherksey *et al.* Applicants respectfully request that this rejection be withdrawn.

#### Obviousness Double Patenting Rejection

The Examiner has rejected claims 3, 30-31, and 33-34 under the doctrine of obviousness-type double patenting in light of the claims of U.S. Patent Application No. 09/396,523.

As an initial matter, Applicants respectfully note that this appears to be a *provisional* rejection since the claims of the other application have not yet been patented. Applicants therefore respectfully request that this rejection be held in abeyance until the claims are otherwise indicated as allowable.

### CONCLUSION

Having addressed all of the rejections, Applicants respectfully submit that the claims may be indicated as allowable, and a notice to that effect is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants' petition for any required relief including extensions of time and authorized the Assistant Commissioner of Patents to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 275102001001.

Dated: June 26, 2002

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## Version with markings to show changes made.

### In the Claims:

Please amend the pending claims as follows:

36. (Amended) A polyamine derivative, or salt thereof, wherein said derivative has the formula  $R_1-X-R_2$ ,

wherein  $R_1-X-$  is of the formula  $R-NH-CR'R''-CO-$ ,

wherein  $-NH-CR'R''-CO-$  is a D- or L- form of valine, asparagine, or glutamine, or the D- form of lysine or arginine[, and];

wherein  $R''$  is H, [or an analogue thereof wherein  $R''$  is]  $CH_3$ ,  $CH_2CH_3$ , or  $CHF_2$ ;

wherein  $R$  is H or a head group selected from the group consisting of a straight or branched  $C_{1-10}$  aliphatic, alicyclic, single or multiring aromatic, single or multiring aryl substituted aliphatic, aliphatic-substituted single or multiring aromatic, a single or multiring heterocyclic, a single or multiring heterocyclic-substituted aliphatic and an aliphatic-substituted aromatic; and

wherein  $R_2$  is a polyamine.

60. (Amended) A method comprising contacting a cell with a polyamine derivative or salt thereof, wherein said derivative has the formula  $R_1-X-R_2$ ,

wherein  $R_1-X-$  is of the formula  $R-NH-CR'R''-CO-$ ,

wherein  $-NH-CR'R''-CO-$  is the L- form of lysine or arginine[, and];

wherein  $R''$  is H, [or an analogue thereof wherein  $R''$  is]  $CH_3$ ,  $CH_2CH_3$ , or  $CHF_2$ ;

wherein  $R$  is H or a head group selected from the group consisting of a straight or branched  $C_{1-10}$  aliphatic, alicyclic, single or multiring aromatic, single or multiring aryl substituted aliphatic, aliphatic-substituted single or multiring aromatic, a single or multiring heterocyclic, a single or multiring heterocyclic-substituted aliphatic and an aliphatic-substituted aromatic; and  $R_2$  is a polyamine

under conditions such that polyamine transport in said cell is inhibited.